DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

January 16, 1990

Dr. Joshua Lederberg
The Rockefeller University
1230 York Avenue
New York, NY 10021-6399

Dear Dr. Lederberg:

Regarding your request for information on the Himalayan mutant and whether it is a temperature-sensitive enzyme or ts-gene regulator, I think it has been shown quite definitively that the mutation in the mouse results from a point mutation at the albino locus (Kwon et al, Biochem Biophys Res Commun 161:252-260, 1989). That point mutation (A>G) results in a residue change (HIS>ARG). Several laboratories (including ours) have now shown that the c-locus encodes an active tyrosinase, thus I think it is safe to assume that the enzyme becomes more temperature sensitive as a result of this alteration. However, the residue affected is far removed from the catalytic domain, transmembrane and other known domains, including putative glycosylation sites, and it is hard to suggest exactly how this mutation might have the observed result, yet there it is. Halaban et al (Proc Natl Acad Sci USA 85:7241-7245, 1988) have suggested that the Himalayan mutation confers a deficiency in N-linked glycosylation which results in an unstable form of the enzyme (which is temperature sensitive). Although this is a nice story and consistent with data obtained, it is not immediately apparent how the point mutation could have such an effect. It is further interesting to note that recent data suggests that the c-locus may not be the sole locus encoding active tyrosinase, since the b-locus (brown) also encodes a less efficient tyrosinase, and there are several other homologous loci that have now been cloned, though not yet sequenced. Thus this whole story is quite fluid at the moment and a subject of great dispute and excitement among those of us in the field. I hope that this has answered your initial question, but if not, or if you now have others, please contact me again. Best wishes and continued success in the New Year.

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Sincerely,

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Thank you very much! This is most helpful. Jon Lederberg

Encl: bill.

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